Claims

Claims

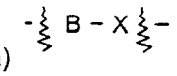
1. A compound according to the formula

A-G-Z-W

or a pharmaceutically acceptable salt, solvates or hydrate thereof, wherein

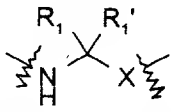
A is $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl-SO_2, $(C_6\text{-}C_{10})$aryl-CH_2-, $(C_6\text{-}C_{10})$arylcarbonyl, $(C_1\text{-}C_9)$heteroaryl, $(C_1\text{-}C_9)$heteroaryl-SO_2-, $(C_1\text{-}C_9)$heteroaryl-CH_2-; or $(C_1\text{-}C_9)$heteroarylcarbonyl;

G is:



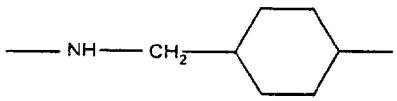
(a)

where B is $(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_9)$heteroaryl, and X is CH_2, SO_2, or carbonyl;



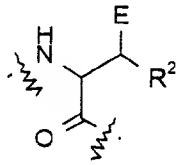
(b)

where X is CH_2, SO_2, or carbonyl; and R^1 and $R^{1'}$ are each independently selected from H, CN, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted; or



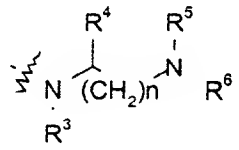
(c) ;

Z is



wherein R^2 is H, $(C_1\text{-}C_8)$alkyl, or is selected from groups A above; and E is selected from groups A above;

W is (a):



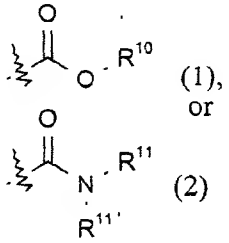
(a)

wherein n is 2-5,

R^3 is selected from H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted;

R^6 is selected from H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted;

R^4 is selected from H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted;or is

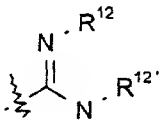


(1), or

(2)

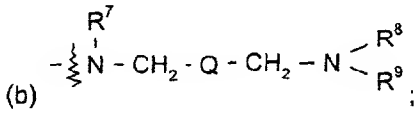
where groups R^{10}, R^{11} and $R^{11'}$ are each, independently, selected from H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted;

R^5 is H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted, or is



wherein R^{12} and $R^{12'}$ are each independently selected from H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted; or

W is (b)



(b)

wherein

Q is selected from the group consisting of $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_3\text{-}C_{10})$cycloalkyl, and $(C_3\text{-}C_{10})$heterocycloalkyl; and

R^7, R^8, and R^9 are each independently selected from H, $(C_1\text{-}C_8)$alkyl-, and phenyl(CH_2)-, wherein said alkyl and phenyl groups are optionally substituted.

2. The compound of claim 1, wherein, independently, one or more of groups A, B, E, and Q therein consist of, or comprise, a $(C_6\text{-}C_{10})$aryl group, selected from phenyl and naphthyl.

3. The compound of claim 1, wherein, independently, one or more of groups A, B, E, and Q therein consist of, or comprise, a $(C_1\text{-}C_9)$heteroaryl group, selected from furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-

triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, and benzoxazinyl.

4. The compound of claim 1, wherein group Q therein is selected from

(a) a (C_6-C_{10})aryl group, selected from phenyl and naphthyl;

(b) a (C_1-C_9)heteroaryl group, selected from furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, and benzoxazinyl;

(c) a (C_3-C_{10})cycloalkyl group, selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,3-cyclobutadienyl, 1,3-cyclopentadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,4-cycloheptadienyl, 1,3,5-cycloheptatrienyl, bicyclo[3.2.1]octane, bicyclo [2.2.1] heptane and the norborn-2-ene unsaturated form thereof; and

(d) a (C_3-C_{10})heterocycloalkyl group, selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxyl, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, and chromanyl.

5. A compound according to claim 1 selected from the group consisting of:

6-Amino-2-[2-[(biphenyl-4-ylmethyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid methyl ester;

2-{3-(3-Fluoro-phenyl)-2-[2-(toluene-4-sulfonylamino)-acetylamino]-propionylamino}-5-guanidino-pentanoic acid methyl ester;

6-Amino-2-[2-[(biphenyl-4-carbonyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid methyl ester;

2-{2-[(Biphenyl-4-carbonyl)-amino]-3,3-diphenyl-propionylamino}-5-guanidino-pentanoic acid methyl ester;

6-Amino-2-[2-[(biphenyl-4-carbonyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

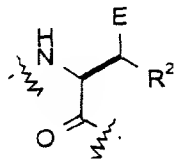
6-Amino-2-[2-(2-benzenesulfonylamino-2-methyl-propionylamino)-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester; and

6. A compound according to claim.5 selected from the group consisting of:

6-Amino-2-[2-[(biphenyl-4-carbonyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester; and

6-Amino-2-[2-(2-benzenesulfonylamino-2-methyl-propionylamino)-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester.

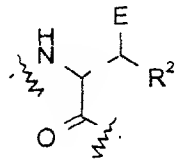
7. A compound according to claim 1, wherein the Z group thereof has the stereospecificity



8. A compound according to claim 7, wherein the Z group defines an L-amino acid selected from the group consisting of L-tryptophanyl, L-histidinyl, L-3-methylhistidinyl, L-phenylalaninyl- L-diphenylalaninyl-, L-2-fluorophenylalaninyl-, L-3-fluorophenylalaninyl-, L-4-fluorophenylalaninyl-, and L-tyrosinyl-.

9. A compound according to claim 8 wherein said Z group thereof is L-tryptophanyl-.

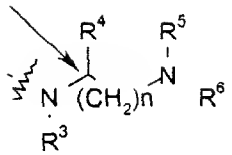
10. A compound according to claim 1, wherein the Z group thereof has the stereospecificity



11. A compound according to claim 10, wherein the Z group defines an D-amino acid that is D-tryptophanyl.

12. A compound according to claim 11 wherein said Z group thereof is D-tryptophanyl-.

13. A compound according to claim 1, wherein the W group thereof has an absolute stereospecific configuration at the indicated position which corresponds to the that of the α-carbon of L-amino acids.



14. A compound according to claim 13, wherein the W group is an L-lysine group or a (C_1-C_8)alkyl ester thereof, an L-ornithine group or a (C_1-C_8)alkyl ester thereof, an L-arginine group or a (C_1-C_8)alkyl ester thereof, an L-histidine group, or a (C_1-C_8)alkyl ester thereof, or an L-3-methylhistidine group, or a (C_1-C_8)alkyl ester thereof.

15. A compound according to claim 14, wherein said W group is a (C_1-C_8)alkyl ester of L-lysine.

16. A compound according to claim 1 wherein R^1 is (C_1-C_8)alkyl- or phenyl(CH_2)- and said alkyl or phenyl group is optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

17. A compound according to claim 1 wherein $R^{1'}$ is (C_1-C_8)alkyl- or phenyl(CH_2)- and said alkyl or phenyl group is optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

18. A compound according to claim 1 wherein R^2 is (C_1-C_3)alkyl-, optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

19. A compound according to claim 1 wherein R^2 is (C_1-C_8)alkyl-, optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

20. A compound according to claim 1 wherein one or more of R^3, R^4, R^5, and R^6 is (C_1-C_8)alkyl- or phenyl(CH_2)-, and said alkyl or phenyl group is optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

21. A compound according to claim 1 wherein one or more of R^7, R^8, and R^9 is (C_1-C_8)alkyl- or phenyl(CH_2)-, and said alkyl or phenyl group is optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

22. A compound according to claim 1 wherein one or more of R^{10}, R^{11}, and $R^{11'}$ is (C_1-C_8)alkyl- or phenyl(CH_2)-, and said alkyl or phenyl group is optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

23. A compound according to claim 1 wherein one or more of R^{12} and $R^{12'}$ is (C_1-C_8)alkyl- or phenyl(CH_2)-, and said alkyl or phenyl group is optionally substituted by one or more halo or trifluoro(C_1-C_8)alkyl groups.

24. A compound according to claim 1 wherein a trifluoro(C_1-C_8)alkyl substituent present on a B, E, R^1, $R^{1'}$, R^2, R^3, R^4, R^5,R^6, R^7, R^8, R^9 ,R^{10}, R^{11}, $R^{11'}$, R^{12} or $R^{12'}$ group thereof is trifluoromethyl.

25. A pharmaceutical composition for increasing growth hormone secretion in a mammal, comprising an effective amount of a compound according to claim 1, and a pharmaceutical carrier.

26. A pharmaceutical composition for increasing secretion of gastrin or glucagon in a mammal, comprising an effective amount of a compound according to claim 1, and a pharmaceutical carrier.

27. A pharmaceutical composition for inhibiting the binding of somatostatin to the sst2 receptor therefor, comprising an effective amount of a compound according to claim 1, and a pharmaceutical carrier.

28. A method for increasing growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 25.

29. A method for increasing secretion of gastrin or glucagon in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 25.

30. A method for decreasing somatostatin-induced downregulation of growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 25.

31. A pharmaceutical composition useful to cause sustained release of growth hormone in a mammal in need thereof, comprising a compound according to claim 1, and a pharmaceutical carrier.

32. A method for facilitating the sustained secretion of growth hormone in a mammal in need thereof, wherein said mammal possesses:

(a) a defect in the expression of the encoding nucleotide sequence for growth hormone, the processing of resultant mRNA, or the translation or intracellular processing and packaging of GH or precursor polypeptide thereof; or

(b) an allele of the growth hormone gene which codes for a growth hormone polypeptide that is insufficiently active;

which comprises administering an effective amount of a pharmaceutical composition according to claim 25.

33. A method for treating a human for one or more symptoms of insufficient growth hormone secretion, wherein said symptom is selected from frailty, hypoglycemia, wrinkled skin, slow skeletal growth, reduced immune function, and reduced organ function, comprising administering an effective amount of a pharmaceutical composition according to claim 25.

34. A method for treating a non-human mammal to enhance the growth and performance thereof, comprising administering an effective amount of a pharmaceutical composition according to claim 25.

35. A pharmaceutical composition according to claim 25 further comprising growth hormone releasing peptide (GHRP) or growth hormone releasing hormone (GHRH).

36. A method for increasing growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 35.

37. A method for increasing growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 25, and a further composition comprising growth hormone releasing peptide (GHRP) or growth hormone releasing hormone (GHRH).

38. A compound according to claim 13, wherein the W group comprises an L-diaminopimelic, L-canavanine, L-2,4-diaminobutyric, L-5-hydroxylysine, or L-epsilon-N-methyllysine group, or a (C_1-C_8)alkyl ester of any thereof.